Tracking trauma-induced structural and functional changes above the level of spinal cord injury

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Abstract: PURPOSE OF REVIEW: This review will highlight the latest findings from neuroimaging studies that track structural and functional changes within the central nervous system at both the brain and spinal cord levels following acute human spinal cord injury (SCI). The putative, underlying biological mechanisms of structural change (e.g. degradation of neural tissue) rostral to the lesion site will be discussed in relation to animal models of SCI and their potential value in clinical studies of human SCI. RECENT FINDINGS: Recent prospective studies in human acute SCI have begun to reveal the time-course, spatial distribution and extent of structural changes following an acute SCI and their relation to functional outcome. Adaptive changes in sensory and motor pathways above the level of the lesion have prognostic value and complement clinical readouts. SUMMARY: The introduction of sensitive neuroimaging biomarkers will be an essential step forward in the implementation of interventional trials in which proof-of-concept is currently limited to clinical readouts, but more responsive measures are required to improve the sensitivity of clinical trials.

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This review will highlight the latest findings from neuroimaging studies that track structural and functional changes within the central nervous system at both the brain and spinal cord levels following acute human spinal cord injury (SCI). The putative, underlying biological mechanisms of structural change (e.g. degradation of neural tissue) rostral to the lesion site will be discussed in relation to animal models of SCI and their potential value in clinical studies of human SCI.

Recent findings
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Summary
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Keywords
atrophy, cortical reorganization, quantitative MRI, spinal cord injury

INTRODUCTION

Spinal cord injury (SCI) is a devastating life event affecting mostly the young (mean age at injury: 33 years) and is 3.8 times more prevalent in men than in women [1]. Worldwide, about 23 cases per million occur annually [2] with tetraplegia slightly more common than paraplegia [1]. In the majority of instances, patients are left with profound and persistent functional impairments such as immediate paralysis, sensory disturbance and the emergence of neuropathic pain at or below the level of injury as a secondary complication [3,4]. A main reason for the limited degree of recovery following SCI relates to failure of the interrupted nerve fiber tracts to regenerate across the lesion site in the adult central nervous system (CNS) of mammals and humans [5]. Important impediments that form the basis of this phenomenon are proteins expressed in CNS myelin (e.g. Nogo-A), which inhibit neurite growth, and the formation of a glial scar that contains extracellular matrix molecules such as chondroitin sulphate proteoglycans [6]. Apart from the failure to regenerate, plastic 'hardware' changes in the adult CNS of mammals and humans are restricted. Experimental treatments against these impediments have resulted in first-in-man phase-I trials for human SCI including anti-Nogo-A antibody treatments [7], stem cell transplantation (HuCNS-SC: NCT01321333 identified in ClinicalTrials.gov) and drug administration (Riluzole: NCT00876889 identified in ClinicalTrials.gov; Minocycline: identified as NCT00559494 in ClinicalTrials.gov; for a review, see [8]). Although much has been learned from these trials, they suffer from a lack of adequate outcome assessments and sensitive biomarkers with the potential to stratify the highly diverse patients into homogenous cohorts and validate the efficacy of drugs [9,10]. To enable efficient translation, these interventions require biomarkers that can be used as surrogate makers of safety and efficacy of agents in a timely and economical manner [11].

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KEY POINTS

- Innovative new multimodal MR protocols allow for the quantification of trauma-induced white and gray matter changes in the spinal cord and the brain above the level of SCI.
- Longitudinal studies in both animals and humans are key to understand the course of structural and functional changes from the acute to the chronic stage of SCI, as well as the prediction of early structural changes and their relation to clinical outcomes.
- Translation between experimental animal models of SCI and clinical (human) SCI will be essential to provide information about the comparability of these models and their ability to distinguish specific disease stages such as how to define the transition from acute to chronic SCI, the dynamic stages of secondary axonal and/or myelin degeneration and training or treatment-induced effects of repair and neural plasticity.

This review addresses the structural and functional plasticity (i.e. secondary, rostral and degenerative structural changes) in both the spinal cord and the brain after SCI against the background of current advances in the field, their relation to clinical outcomes as well as challenges and future avenues in clinical SCI research.

HUMAN SPINAL CORD INJURY: NONINVASIVE TRACKING OF TRAUMA-INDUCED CHANGES

Conventional magnetic resonance imaging (MRI) remains the gold standard for identifying the localization and the extent of an SCI [12,13] but does not allow for the quantification of trauma-induced disruption to the microstructure of the spinal cord and supraspinal changes. Novel quantitative MRI protocols of the spinal cord and brain have the potential to measure neural changes at the microstructural level. This is because the degree of myelination, iron content and neuronal microstructure are reflected in MR relaxation times, magnetization transfer and diffusion-weighted images which can be measured at high resolution [14–16]. These novel quantitative MR methods include multiparametric mapping [17–21] and diffusion tensor imaging [22] next to volumetric measures (i.e. voxel-based morphometry [23]) and voxel-based cortical thickness [24].

Structural changes

By means of computational anatomy, trauma-induced structural changes have been revealed across the entire neuroaxis. In chronic SCI patients, cervical cross-sectional cord area, rostral to the site of injury, was reduced by up to 30% and white matter integrity within the corticospinal tracts altered [25–27]. Further upstream, structural changes in terms of volume and microstructure within the white matter of the pyramids and internal capsule paralleled those of the spinal cord [28]. At the cortical level, the primary sensorimotor cortices were atrophied [25,29,30]. The question of the temporal evolution and spatial specificity of these atrophic changes was addressed in a recent longitudinal study in acute SCI patients ([31]; see Fig. 1). Extensive upstream structural changes appeared already within the first months after injury as reflected by a decrease in cervical spinal cord area (see Fig. 1a/b), white matter volume of the corticospinal tracts at the level of internal capsule and right cerebral peduncle and gray matter volume in M1 (see Fig. 1c/d). Importantly, clinically eloquent relationships between structural spinal and brain changes of the sensorimotor system have been demonstrated. Specifically, the amount of motor and sensory disability, as assessed by the international standards for the neurological classification of SPI protocol [32], was directly associated with the degree of spinal [27,33,34] and brain atrophy [29,35]. Moreover, a decrease in the left-right diameter of the cervical cord area correlated with the motor score and the anterior-posterior diameter with the sensory score [34], indicating tract-specific atrophy. These clinically eloquent structural changes along the neuroaxis are suggestive of axonal degeneration and demyelination of the corticospinal tracts and the volume reduction at the cortical level reflect soma shrinkage of injured corticomotor neurons [36].

Functional changes

Next to trauma-induced structural changes, brain (neural) activity in SCI – revealed by functional MRI ndash; has shown motor task-related activation in the primary motor cortex (M1) and associated cortical motor areas in the subacute phase of SCI [37]. In the transition from acute to chronic SCI, the area of M1 activation increased, whereas associated sensorimotor areas (e.g. supplementary motor areas) showed a progressive decrease in activation [37]. Studies in chronic SCI patients indicate that the deafferented M1 regions remain hyperexcitable during motor stimulation [38]. Loss of motor input was shown to induce an expansion of the M1 hand area of paraplegic and tetraplegic patients into the output-deprived M1 leg area [25,39,40]. However, whether these changes translate into functional output is questionable as stimulations of corticomotor neurons by transcranial

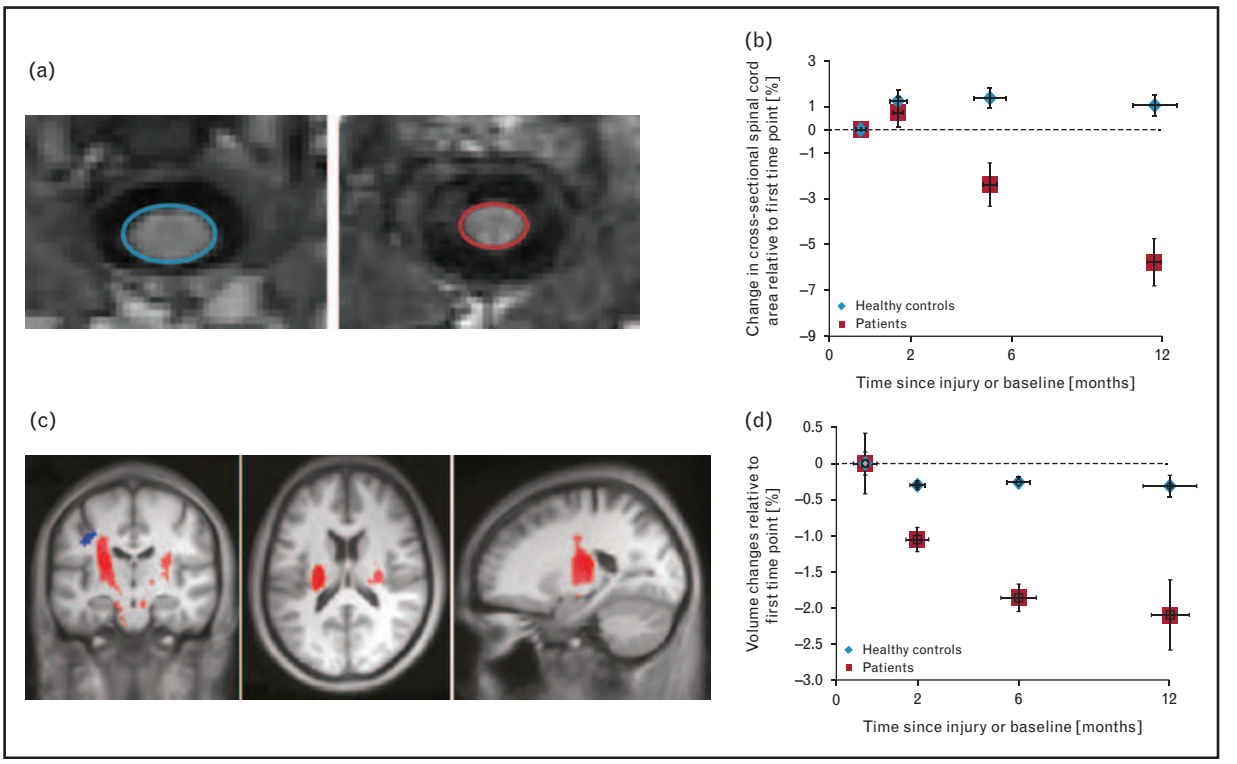

FIGURE 1. (a)/(b) Progressive structural changes of the injured spinal cord. (a) Representative example of a healthy control (spinal cord area highlighted in blue) and a chronic SCI patient (spinal cord area highlighted in red). (b) Change in cross-sectional spinal cord area differed significantly between patients and controls. Error bars show the standard errors of the scan intervals (horizontal) and of the percentage change in cross-sectional spinal cord area (vertical). (c)/(d) Longitudinal changes in local brain volume as revealed by tensor-based morphometry. (c) Statistical parametric map including the cranial corticospinal tract and the bilateral sensorimotor cortex (uncorrected $P < 0{\cdot}001$, shown for descriptive purposes). Regions of volume changes are highlighted in blue (gray matter) and red (white matter). (d) Changes in white matter volume in the corticospinal tracts, at the level of the left internal capsule, in patients and healthy controls over time. Error bars show the standard errors of the scan intervals (horizontal) and of the percentage change in spinal cord area (vertical). Adapted with permission from [31].

magnetic stimulation (TMS) above the M1 leg area did not elicit hand/arm muscle activation [41].

Interestingly, a recent study showed in incomplete paraplegics patients that performance improvements through intensive virtual reality augmented coordination and balance training of foot and leg movements were directly linked to local volume increases in cortical and subcortical areas associated with learning and motor performance [42].

Brain reorganization may not only be related to functional recovery, but could also be associated with sensory disturbances as there is increasing evidence relating thalamic and cortical changes to the generation and/or maintenance of neuropathic pain below the level of injury [30,43]. Functional and structural alteration in terms of decreased activity in the atrophied thalamus [29], as well as decreased cortical activity in frontal areas and possibly increased subcortical activity have been related to pain ([44–47]; for a review, see [48]).

Although the underlying mechanisms are uncertain, Qiu *et al.* [49] described that repetitive TMS treatment over M1 leads to a substantial pain relief in a patient who suffered from deafferentation pain for more than 20 years. Interestingly, glucose metabolism was significantly reduced at the contralateral anterior cingulate cortex, insula and caudate nucleus after treatment, which might indicate some type of short-term plasticity induction [49]. As treatment over M1 was also shown to be effective for other chronic pain states [50–52], this treatment might be promising for future clinical applications. However, double-blinded studies with larger sample sizes are needed to understand the functional changes at brain level and their effect on pain [53].

Summary

In conclusion, these new findings from neuroimaging studies in human SCI indicate progressive long-

distance fiber degeneration along the sensorimotor system, structural cortical reorganization with a typical temporal and spatial course and a close relationship between the degree of structural and functional changes to clinical measures of impairment and outcome.

ANIMAL MODELS OF SPINAL CORD INJURY: INVASIVE TRACKING OF TRAUMA-INDUCED CHANGES

Although neuroimaging outcome measures can track trauma-induced structural changes and functional reorganization in human SCI, they cannot reveal the biological processes underlying these changes (i.e. degeneration/demyelination vs. regeneration/remyelination and cortical reorganization). The pathological processes underlying these changes are not fully resolved, but in principal underlying mechanisms of spinal cord damage and regeneration/repair are assumed to be rather similar between animal models of SCI and human SCI [54]. Both are characterized by remote axonal damage and demyelination of white matter tracts [55], the evolution of the lesion area (i.e. cyst formation) [56], cortical reorganization [31] and the inherent low capacity of repair [57]. In particular, rodent and primate models of SCI have demonstrated progressive axonal anterograde and retrograde degeneration of spinal pathways with subsequent neuronal changes at multiple levels [58–60].

When investigating acute stages of SCI, not only the spinal cord circuitries react immediately to the injury [61], but also cortical reorganization occurs as early as hours after thoracic hemisection in responses to electrical stimuli to the intact forepaw [62▪,63▪], previously only shown in chronic SCI rodents [64,65]. This enlargement of cortical S1 area appeared as early as 3 days after injury [63▪,66], and 7 days after injury the performance of tested animals was proportional to the reorganization at 1 day after injury [63▪] (see Fig. 2 [62▪]). In accordance, resting-state functional MRI showed alterations in spontaneous neuronal activity in several brain regions in monkeys [67] as well as in rats [62▪] with a thoracic hemisection. These observations might further help to understand the pathophysiological mechanisms behind these changes.

Furthermore, recent longitudinal studies showed that disintegration of the spinal cord spreads rostrally and caudally with a tendency to reduced spinal cord diameters 12 weeks after injury as shown in Fig. 3 [67,68], as in human SCI [25,34]. In addition, cortical reorganization of S1 increased over time and correlated with the rostral, anterio-posterior diameter of the spinal cord indicating that a more severe SCI leads to greater cortical reorganization. This is in line with Yang *et al.* [69] who showed that not only the severity of injury correlated with the extent of early cortical plasticity in the sensory cortices, but also to the severity of late behavioral deficits. The investigation of cortical activation after electrical forepaw stimulation represents one reliable method for tracking the cortical reorganization. As somatosensory evoked potentials (SSEPs) are already routinely used in patients, Bazley *et al.* [70▪] showed that SSEPs are able to detect significant enhancements in activation of forelimb sensory pathways in rats with SCI at the thorax level, indicating that this method might also be useful for assessing treatments that modulate plasticity after SCI. Moreover, Sydekum *et al.* [63▪] showed a significant latency difference at the ipsilateral S1 cortex on day 7. This might predict, at least in rats, the time at which the brain undergoes the most adaptions which might be a promising time window for therapeutic strategies such as rehabilitation [70▪].

CONCLUSION

At present, neuroimaging biomarkers are still not used routinely in human SCI to assess the efficacy of interventions (physical therapies or drugs) and how they relate to compensatory neuronal processes at the spinal cord and brain level. The proposed neuroimaging biomarkers have shown their potential to provide novel insights specifically wherein clinical measures might be insensitive to reveal subtle changes of spinal cord and brain function. However, these subtle changes ultimately may become valued as a proof-of-concept in which an amplification of the effectiveness eventually may translate into clinically meaningful changes of functional outcomes. The establishment of quantifiable and specific surrogate markers in animal models and human SCI will be essential to inform about the comparability of these models in the sense of disease stage (what indicate the transition from an acute to a chronic SCI, what stages of chronic SCI can be distinguished), extent of axonal/myelin damage and effects of repair/neural plasticity. Ultimately, quantitative and functional MRI in longitudinal multicenter assessments in acute SCI are required that measure central spinal and brain sequels simultaneously [71] and their impact on cortical reorganization as SCI patients recover. This should allow the identification of the most sensitive imaging markers and their applicability in clinical trials.

Future directions

From a clinical perspective, the relationships between the extent of the spinal cord lesion, the amount of

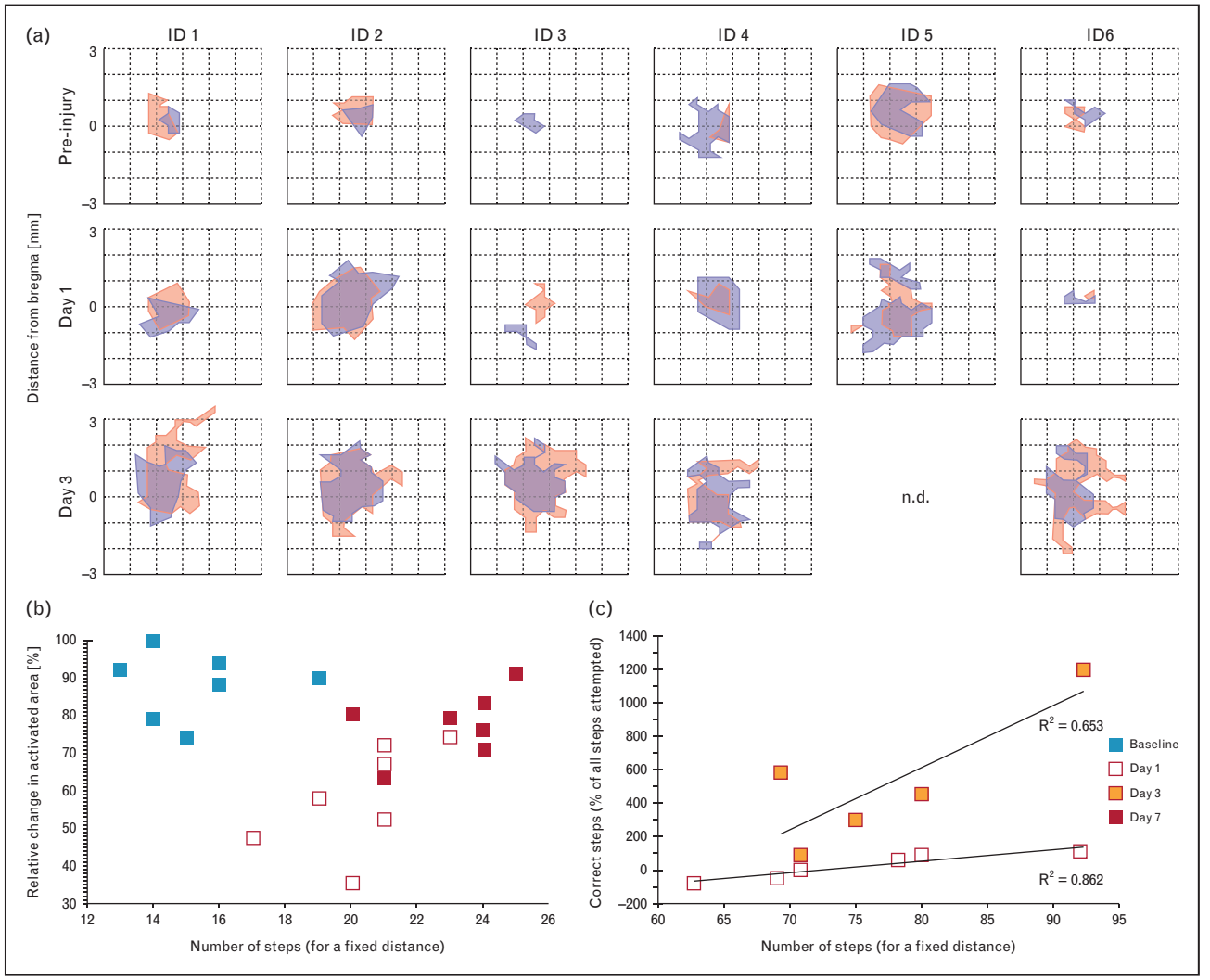

FIGURE 2. (a) Individual task-related brain activity maps within the forelimb representations for intact animals and SCI animals over time. BOLD-fMRI maps of forelimb representations in the sensory-motor cortex, intact and after injury for six individual rats monitored. Maps (upper: red, lower: blue) are displayed at uniform intensity levels and semitransparent to visualize overlaps. Maps are displayed for the 1.6 mA (intact, 1, 3, 7 days postinjury) stimulation strength. In the coordinate space, x-axis denotes lateral distance from the midline (in mm) and y-axis distance from bregma (in mm). (b)/(c) Effects on spinal cord injury (thoracic level T8) on skilled forelimb function. (b) Success rate quantified as percentage of correct steps among all of the attempted steps while crossing the horizontal ladder as a function of the number of steps required for a fixed distance. Symbols represent values measured as baseline (blue squares), 1 (open squares) and 7 days following SCI (red squares). (c) Success rate in forelimb use at day 7 as a function of change in activation area as derived from BOLD fMRI signal on day 1 (open squares) and days 3 (red squares with orange filling) with respect to baseline values. The correlation coefficients are indicated in the figure. Adapted with permission from [62▪].

cortical reorganization and the recovery of behavior need to be further investigated in serial studies [72]. Animal models will help us understand not only the influence and ensuing consequences of different lesions, but also which neuroimaging outcome measures have predictive value. The continuous developments in the rapidly evolving field of spinal cord MRI at high resolution will help in detecting and understanding the structural changes below, within and above a SCI. Novel, improved MRI sequences and automated image processing methods [73–76] have shown the potential to accurately distinguish (separate) gray and white matter at the spinal level and assess spinal activation patterns [77]. These advances will help us to better define the lesion level, extent of the injury and tracts affected.

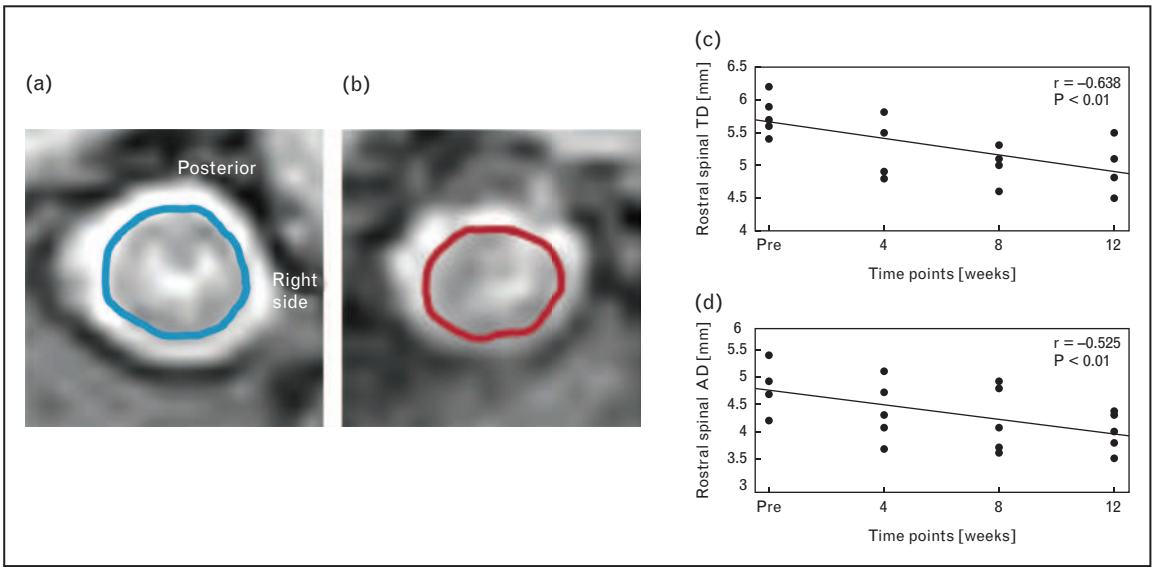

FIGURE 3. (a)/(b) Progressive structural changes of the injured spinal cord. (a) Representative example of a healthy nonhuman primate (spinal cord area highlighted in blue) at thoracic level. (b) MRI of the injured region in a nonhuman primate model of spinal cord injury (thoracic level T7–T9). Cross-sectional rostral spinal cord area (highlighted in red) assessed 2 cm above the lesion at 12 weeks after SCI. (c)/(d) Correlations among the rostral transverse (TD) and anterior-posterior diameter (AD) of the spinal cord at different time points after lesion. The y-axis in each diagram indicates the measured diameter of the spinal cord at different locations, and the x-axis is the time point. The correlation coefficients are indicated in the figure. Adapted with permission from [67].

Current work in our laboratory is focusing on improving the MR sequences and postprocessing pipelines. The primary aim will be to extend our existing brain image segmentation approach to use atlas data from both head and neck [76]. This would allow clinicians to better assess MRI data of patients with SCI and patients with neurological diseases involving the spinal cord. Moreover, anatomical MRI scans of the head and neck, collected at multiple time points following a spinal incidence such as trauma, allow longitudinal changes in terms of both rates of change (i.e. velocity) and its acceleration or deceleration (e.g. atrophy rates and possible recovery) to be determined more accurately via longitudinal image registration procedures [78].

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Conflicts of interest

There are no conflicts of interest.

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